

WHAT IS CLAIMED IS:

1. A biologically active peptide consisting essentially of the formula selected from:

5 (a) $X_{01}\text{Val}X_{02}\text{Glu}\text{Ile}\text{Gln}\text{Leu}\text{Met}\text{His}X_{03}X_{04}X_{05}X_{06}X_{07}$ (SEQ. ID. NO.1);
(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12, or 1-13;
(c) pharmaceutically acceptable salts of (a) or (b); or
(d) N - or C-derivatives of (a), (b) or (c);

wherein:

10 X_{01} is an α -helix-stabilizing residue, Gly, Ser or Ala;

X_{02} is an α -helix-stabilizing residue, Ala or Ser;

X_{03} is Ala, Gln or Asn;

X_{04} is Arg, Har or Leu;

X_{05} is an α -helix stabilizing residue, Ala or Gly;

X_{06} is an α -helix stabilizing residue or Lys;

15 X_{07} is an α -helix stabilizing residue, Trp or His;

wherein at least one of X_{01} , X_{02} , X_{05} , X_{06} or X_{07} is an α -helix stabilizing residue, and wherein at least one of said α -helix stabilizing residues is Aib, Ac_3c , Ac_4c , Ac_5c , Ac_6c , or Deg.

20 2. The peptide of claim 1, wherein said peptide is selected from:

20 (a) $\text{Ala}\text{Val}\text{Deg}\text{Glu}\text{Ile}\text{Gln}\text{Leu}\text{Met}\text{His}\text{Gln}\text{Har}\text{Ala}\text{Lys}\text{Trp}$ (SEQ. ID. NO. 37);
(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
(c) pharmaceutically acceptable salts of (a) or (b); or
(d) N - or C - derivatives of (a), (b) or (c).

25 3. The peptide of claim 1, wherein said peptide is selected from:

25 (a) $\text{Ala}\text{Val}\text{Ac}_3\text{c}\text{Glu}\text{Ile}\text{Gln}\text{Leu}\text{Met}\text{His}\text{Gln}\text{Har}\text{Ala}\text{Lys}\text{Trp}$ (SEQ. ID. NO. 38);
(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
(c) pharmaceutically acceptable salts (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

4. The peptide of claim 1, wherein said peptide is selected from:

(a) AlaValAc₃cGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 39);

5 (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

5. The peptide of claim 1, wherein said peptide is selected from:

10 (a) DegValAlaGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 24);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

6. The peptide of claim 1, wherein said peptide is selected from:

15 (a) DegValDegGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 27);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

20 7. The peptide of claim 1, wherein said peptide is selected from:

40; (a) DegValAc₃cGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO.

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

25 (d) N - or C - derivatives of (a), (b) or (c).

8. The peptide of claim 1, wherein said peptide is selected from:

5 (a) DegValAc₃cGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 41);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

9. The peptide of claim 1, wherein said peptide is selected from:

10 (a) DegValAibGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 42);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

15 10. The peptide of claim 1, wherein said peptide is selected from:

(a) Ac₃cValAlaGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 25);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

20 11. The peptide of claim 1, wherein said peptide is selected from:

(a) Ac₃cValDegGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 43);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

25 12. The peptide of claim 1, wherein said peptide is selected from:

(a) Ac₃cValAc₃cGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 28);

- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
- (c) pharmaceutically acceptable salts (a) or (b); or
- (d) N - or C - derivatives of (a), (b) or (c).

13. The peptide of claim 1, wherein said peptide is selected from:

5 (a) $\text{Ac}_3\text{cValAc}_5\text{cGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 44);

- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 1-13;
- (c) pharmaceutically acceptable salts (a) or (b); or
- (d) N - or C - derivatives of (a), (b) or (c).

10 14. The peptide of claim 1, wherein said peptide is selected from:

(a) $\text{Ac}_3\text{cValAibGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 45);

- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- (d) N - or C - derivatives of (a), (b) or (c).

15 15. The peptide of claim 1, wherein said peptide is selected from:

(a) $\text{Ac}_5\text{cValAlaGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 4);

- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- (d) N - or C - derivatives of (a), (b) or (c).

20 16. The peptide of claim 1, wherein said peptide is selected from:

(a) $\text{Ac}_5\text{cValDegGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 46);

- (b) peptides containing amino acids 1-9,1-10, 1-11, 1-12 or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- (d) N - or C - derivatives of (a), (b) or (c).

17. The peptide of claim 1, wherein said peptide is selected from:

(a) $\text{Ac}_5\text{cValAc}_3\text{cGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 47);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

5 18. The peptide of claim 1, wherein said peptide is selected from:

(a) $\text{Ac}_5\text{cValAc}_3\text{cGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 29);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

10 19. The peptide of claim 1, wherein said peptide is selected from:

(a) $\text{Ac}_5\text{cValAibGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 15);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12, or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

15 20. The peptide of claim 1, wherein said peptide is selected from:

(a) $\text{AibValDegGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 48);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

25 21. The peptide of claim 1, wherein said peptide is selected from:

(a) $\text{AibValAc}_3\text{cGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 49);

- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- (d) N - or C - derivatives of (a), (b) or (c).

22. The peptide of claim 1, wherein said peptide is selected from:

- 5 (a) AibValAc5cGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 50);
- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- (d) N - or C - derivatives of (a), (b) or (c).

10 23. The peptide of claim 1, wherein said peptide is selected from:

- 51 (a) Ac5cValSerGluIleGlnLeuMetHisGlnHarAlaLysTrp (SEQ. ID. NO. 51);
- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- 15 (d) N - or C - derivatives of (a), (b) or (c).

24. The peptide of claim 1, wherein said peptide is selected from:

- 52 (a) Ac5cValSerGluIleGlnLeuMetHisAsnLeuGlyLysHis (SEQ. ID. NO. 52);
- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12, or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- 20 (d) N - or C - derivatives of (a), (b) or (c).

25. The peptide of claim 1, wherein said peptide is selected from:

- (a) Ac5cValAlaGluIleGlnLeuMetHis (part of SEQ. ID. NO. 4);
- (b) pharmaceutically acceptable salts thereof; or
- 25 (c) N - or C - derivatives of (a) or (b).

26. A biologically active peptide consisting essentially of the formula selected

from:

- (a) $X_{01}ValX_{02}GluIleX_{03}LeuMetHisX_{04}X_{05}X_{06}LysX_{07}$ (SEQ. ID. NO. 5);
- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12, or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- (d) N - or C - derivatives of (a), (b) or (c);

5

wherein:

X_{01} is α -helix-stabilizing residue, Gly, Ser or Ala;

X_{02} is α -helix-stabilizing residue, Ala or Ser;

X_{03} is Ala, Gln or Asn;

10

X_{04} is Ala, Gln, Asn, Har or Arg;

X_{05} is an α -helix stabilizing residue, Ala or Gly;

X_{06} is an α -helix stabilizing residue or Lys;

X_{07} is α -helix stabilizing residue, Trp, or His;

15

wherein at least one of X_{01} , X_{02} , X_{05} , X_{06} or X_{07} is an α -helix stabilizing residue,

1

and wherein at least one of said α -helix stabilizing residues is Aib, Ac_3c , Ac_4c , Ac_5c , Ac_6c , or Deg.

27. The peptide of claim 26, wherein said peptide is selected from:

20

- (a) $Ac_4cValAibGluIleGlnLeuMetHisGlnHarAlaLysTrp$ (SEQ. ID. NO. 7);
- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- (d) N - or C - derivatives (a), (b) or (c).

25

28. The peptide of claim 26, wherein said peptide is selected from:

- (a) $Ac_6cValAibGluIleGlnLeuMetHisGlnHarAlaLysTrp$ (SEQ. ID. NO. 8);
- (b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;
- (c) pharmaceutically acceptable salts of (a) or (b); or
- (d) N - or C - derivatives of (a), (b) or (c).

29. The peptide of claim 26, wherein said peptide is selected from:

(a) $\text{Ac}_5\text{cVal Ac}_4\text{cGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 9);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives (a), (b) or (c).

30. The peptide of claim 26, wherein said peptide is selected from:

(a) $\text{Ac}_5\text{cValAc}_6\text{cGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 10);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

31. The peptide of claim 26, wherein said peptide is selected from:

(a) $\text{Ac}_4\text{cValAc}_4\text{cGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 11);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

32. The peptide of claim 26, wherein said peptide is selected from:

(a) $\text{Ac}_6\text{cValAc}_6\text{cGluIleGlnLeuMetHisGlnHarAlaLysTrp}$ (SEQ. ID. NO. 12);

(b) peptides containing amino acids 1-9, 1-10, 1-11, 1-12 or 1-13;

(c) pharmaceutically acceptable salts of (a) or (b); or

(d) N - or C - derivatives of (a), (b) or (c).

25 33. The peptide of claim 1 or 26, wherein said peptide is labeled with a label selected from the group consisting of a fluorescent label, a chemiluminescent label, a bioluminescent label and a radioactive label.

34. The peptide of claim 1 or 26, wherein said peptide is labeled with ^{125}I .
35. The peptide of claim 1 or 26, wherein said peptide is labeled with $^{99\text{m}}\text{Tc}$.
36. A pharmaceutical composition comprising the biologically active peptide of claim 1 or 26, and a pharmaceutically acceptable carrier.
- 5 37. A method for treating mammalian conditions characterized by decreases in bone mass, said method comprising administering to a subject in need thereof an effective bone-mass increasing amount of a biologically active peptide of claim 1 or 26.
- 10 38. A method for treating mammalian conditions characterized by decreases in bone mass, said method comprising administering to a subject in need thereof an effective bone mass-increasing amount of a composition comprising a biologically active peptide of claim 1 or 26 and a pharmaceutically acceptable carrier.
- 15 39. A method for determining rates of bone reformation, bone resorption and/or bone remodeling comprising administering to a patient an effective amount of a peptide of claim 1 or 26 and determining the uptake of said peptide into the bone of said patient.
40. The method of claim 37, wherein said condition to be treated is hyperparathyroidism.
- 20 41. The method of claim 37, wherein said condition to be treated is hypercalcemia.
42. The method of claim 37, wherein said effective amount of said peptide for increasing bone mass is from about $0.01\mu\text{g}/\text{kg}/\text{day}$ to about $1.0\mu\text{g}/\text{kg}/\text{day}$.

-45-

43. The method of claim 37, wherein the method of administration is parenteral.

44. The method of claim 37, wherein the method of administration is subcutaneous.

5 45. The method of claim 37, wherein the method of administration is nasal insufflation.

46. The method of claim 37, wherein the method of administration is oral.

47. The method of making the peptide of claim 1 or 26, wherein said peptide is synthesized by solid phase synthesis.

10 48. The method of making the peptide of claim 1 or 26, wherein said peptide is synthesized by liquid phase synthesis.

49. The method of making the peptide of claim 1 or 26, wherein said peptide is protected by Fmoc.